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Literature Review: Integration Of Molecular Docking, ADMET Prediction, And Chemical Modification Of Indonesian Natural Compounds As Anticancer Candidates

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Abstract

As one of the highest drivers of mortality at the global level, cancer is identified through unregulated cell proliferation. This condition urges researchers to immediately find new therapeutic agents that have a superior safety and efficacy profile. This review analyzes the (CADD) approach, especially the integration of molecular docking, ADMET prediction, and chemical modification, as an important strategy in exploring Indonesian natural product compounds as anticancer candidates. This research aims to review the integrative role of these three approaches in increasing the potential of natural compounds as lead compounds. The method used is a systematic literature review from the Google Scholar and PubMed databases. The results of a review of various studies show that the in silico approach via molecular docking has succeeded in identifying potential compounds such as squalene, berberine, and quercetin with high binding affinity to cancer targets such as NUDT5, HER2, and EGFR. ADMET prediction and drug-likeness testing (Lipinski's Rule) confirm the pharmacokinetic and safety profiles of drug candidates. Furthermore, chemical modifications to lead compounds such as curcumin and gallic acid were proven to increase significantly stability and cytotoxic activity. The integration of this method makes an important contribution in accelerating the discovery of new drugs, reducing research costs, and increasing the opportunities.

Keywords: Molecular docking; ADMET; Chemical modification; Natural compounds; Anticancer.

INTRODUCTION

Cancer is a complex disease characterized by uncontrolled proliferation of abnormal cells, the ability to invade tissue, and metastasis to other organs. This disease is one of the leading causes of death worldwide, with the global burden continuing to increase annually. Data from the World Health Organization (WHO) in 2020 recorded a cancer incidence of 19.3 million people, with a death toll approaching 10 million. This trend is expected to continue to soar, surpassing 28 million cases by 2040. Furthermore, currently available cancer therapies still face various limitations, such as drug resistance, high side effects, and low selectivity for cancer cells compared to normal cells. Therefore, the development of new, more effective and safe drug candidates is necessary (Vasan et al., 2022).

The richness of natural secondary metabolites is a key foundation in the search for new cancer drugs, supported by the variety of structural designs and the spectrum of biological activity they possess. A study by David J. Newman shows that natural products remain a major contributor to modern drug discovery, including in cancer therapy (Newman, 2022). Compounds such as alkaloids, flavonoids, terpenoids, and polyphenols have been shown to possess cytotoxic activity against various types of cancer cells through mechanisms such as apoptosis induction and inhibition of cell proliferation (Atanasov et al., 2022). Indonesia, as a country with very high biodiversity, has great potential for exploring bioactive compounds, but their utilization in drug development based on modern approaches is still not optimal.

Conventional drug development is generally time-consuming, expensive, and has a high failure rate, especially during clinical trials. To address these challenges, computational approaches, or computer-aided drug discovery (CADD), are increasingly being used in modern pharmaceutical research. One of the key methods in CADD is molecular docking, which enables rapid and efficient prediction of interactions between ligands and target proteins (Pinzi & Rastelli, 2022). This technique is used to evaluate binding affinity and molecular orientation within the active site of the target protein, thus identifying potential compound candidates early in the research process (Ferreira et al., 2022). In the context of cancer, molecular docking has been widely used to target key proteins such as EGFR,

HER2, and various kinases that play a role in cancer cell proliferation.

Although molecular docking can identify a compound's potential biological activity, successful drug development is determined not only by its affinity for the target but also by its pharmacokinetic and toxicity profiles. Many candidate compounds fail at advanced stages because their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties do not meet drug-safety criteria. Therefore, in silico ADMET prediction has become a crucial component of the modern drug discovery process (Daina et al., 2022). Tools such as SwissADME and pkCSM enable rapid and accurate evaluation of a compound's drug-likeness, bioavailability, and potential toxicity (Pires et al., 2023). This approach can reduce the risk of failure in the preclinical and clinical stages, thereby increasing the efficiency of the drug development process.

On the other hand, natural compounds often have limitations, such as low stability, poor solubility, and low bioavailability. Therefore, chemical modification is an important strategy to enhance the potency of these compounds. Modification can be achieved through analog synthesis, functional group derivatization, or semi-synthetic approaches to produce compounds with higher biological activity and improved pharmacokinetic properties. For example, structural modification of curcumin has produced various analogues with improved anticancer activity, stability, and bioavailability compared to the parent compound (Afzal et al., 2022).

Although molecular docking, ADMET prediction, and chemical modification have been widely used individually, the integration of these three approaches within a single research framework is still relatively limited, particularly in the exploration of Indonesian natural product compounds. This integrative approach holds great potential for improving efficiency and accuracy in the drug discovery process, from initial candidate identification to compound structure optimization (Zhang et al., 2023). This integration enables the selection of compounds that not only have high affinity for the target but also have favorable pharmacokinetic profiles and optimal biological activity.

Based on this background, this article aims to systematically review the role of integrated molecular docking, ADMET prediction, and chemical modification in the development of Indonesian natural product compounds as anticancer candidates. This review is expected to provide a comprehensive understanding of modern natural product-based drug discovery strategies and serve as a foundation for further research in medicinal chemistry and computational pharmacy.

RESEARCH METHODS

This study employed a descriptive-qualitative literature review with an exploratory nature. The data collection process explored various scientific literature systematically accessed through Google Scholar and PubMed. The articles reviewed were published between 2022 and 2026, written in English or Indonesian, and available in full-text form. Keywords used in the search process included "molecular docking," "ADMET," "chemical modification," "natural compounds," and "anticancer." Inclusion criteria included journal articles published within the relevant timeframe, focusing on the exploration of Indonesian natural compounds, molecular dynamics simulations, and chemical structure modification for anticancer activity. A total of 11 primary articles were analyzed in depth to summarize recent developments in this field.

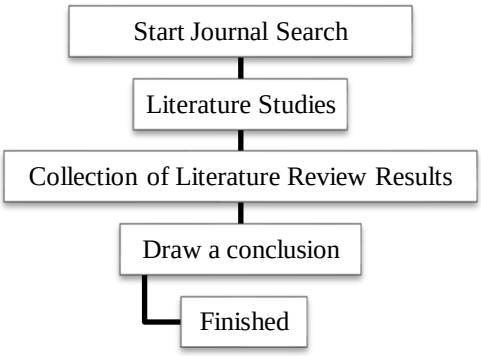

Figure 1. Research flow

RESULTS AND DISCUSSION

A literature search using the Google Scholar and PubMed databases yielded 2,133 articles, comprising 291 articles from Google Scholar and 1,842 articles from PubMed, covering the period 2022–2026. A selection process, including title and abstract screening, identified 47 relevant articles. Further screening reduced the number of articles to 27 that met the initial criteria. After a full-text feasibility evaluation, 25 articles were identified as relevant to the research topic.

Of these articles, 11 were selected for further analysis based on their relevance to the study's focus, namely the role of computational medicinal chemistry in identifying anticancer candidates through a molecular docking approach on natural product compounds. Articles that did not meet the inclusion criteria or had incomplete data were excluded from the analysis. Based on the publication language, the articles analyzed consisted of 5 Indonesian articles and 6 English articles.

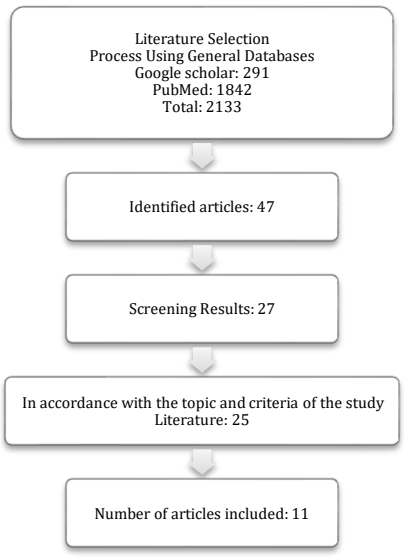

Figure 2. Literature Search Flowchart

This study analyzed 11 articles obtained through literature screening from several scientific databases, namely Google Scholar and PubMed. Article selection was based on predetermined inclusion criteria, particularly their relevance to the topic of the role of computational medicinal chemistry in identifying anticancer candidates through a molecular docking approach on natural product compounds. The results of the analysis of these articles are then presented briefly in Table 1.

Table 1. Literature Review Results Related to Molecular Docking Integration, ADMET Prediction, and Modification Chemistry of Indonesian Natural Compounds as Anticancer Candidates

No.	Title	Writer	Method	Results
1.	The Role of Computational Medicinal Chemistry in Identification of Anti-Cancer Agents through Molecular Docking of Natural Compounds	(Amin et al., 2025)	Molecular Docking (PLANTS), Molecular Dynamics Simulation (10 ns), ADMET Analysis (pkCSM), Drug-likeness Test (Lipinski's Rule of Five), In silico	The in silico approach successfully identified several potential candidates such as squalene (very high affinity to NUDT5) and Tetradec-13-en-11-yn-1-ol.
2.	Applications of molecular docking in natural products-based drug discovery	(Asiamah et al., 2023)	Integration of computer-aided drug discovery (CADD) techniques such as molecular docking	The use of molecular docking in natural product research helps predict the success of phytochemicals, saves time and costs, and enables the discovery of new uses for medicinal plants (repurposing).
3.	Molecular Docking Study and ADMET Prediction of Curcumin Derivative Compounds as Casein Kinase 2-α Inhibitors	(Hakiki et al., 2024)	AutoDock Tools 1.5.7 against the target Casein Kinase 2-α (PDB ID: 3PE1). The study was continued with Lipinski's Rule of Five testing and ADMET screening using SwissADME and admetSAR.	The three best curcumin derivatives are Di-O-acetyldemethoxycurcumin (ΔG = -10.13 kcal/mol), Dimethoxycurcumin (-9.93 kcal/mol), and Dimethylcurcumin (-9.88 kcal/mol). All three meet Lipinski's criteria and are predicted to have strong potential as Casein Kinase 2-α inhibitors for leukemia.
4.	In-silico Toxicity Prediction of Phenolic Compounds of Artemisia annua as Anticancer Drug Candidate	(Sari et al., 2024)	Toxicity prediction (mutagenicity, carcinogenicity, hepatotoxicity, and acute toxicity) was performed using the Protox II web application, Vega QSAR, and pkCSM. Physicochemical properties were predicted using SwissADME.	Of the 36 phenolic compounds from A. annua, 29 met Lipinski's parameters and had potential as oral drugs. Although not hepatotoxic, 19 compounds were predicted to be mutagenic and carcinogenic, with quercetin being the most toxic compound based on its LD50 value.
5.	Exploration of Natural Compounds as Lead Anti-Breast Cancer	(Amin et al., 2024)	Molecular docking (AutoDock Vina, PyRx), ADMET prediction (SwissADME, pkCSM), and	The compounds berberine, ellagic acid, camptothecin, and kaempferol showed high binding affinity to important

	Agents Using an In Silico Approach		molecular dynamics simulation (GROMACS)	breast cancer targets such as HER2, ER, PR, and PD-L1.
6.	Chemical Modification of Curcumin into Its Semi-Synthetic Analogs Bearing Pyrimidinone Moiety as Anticancer Agents	(Afzal et al., 2022)	Synthesis of three new curcumin analogs (C1-C3), followed by analytical characterization, evaluation of anticancer activity against 59 NCI cancer cell lines, and molecular docking studies against the EGFR receptor	The C2 analog showed significant growth inhibitory activity on various cancer cell lines, and docking results visualized its stable interaction at the active site of EGFR with a binding energy of -5.086 kcal/mol.
7.	Exploration of Indonesian Medicinal Plants as Anti-Breast Cancer Candidates through a Medicinal Chemistry Approach	(Amin & Fauziyyah, 2025)	Medicinal chemistry approach, molecular docking (In silico), ADMET (or ADME/Tox)	Various Indonesian bioactive compounds such as moringin isothiocyanate (moringa), andrographolide (sambiloto), quercetin (purple kencana), galangin (galangal), zingiberenol (ginger), and sesamin (babandotan) have strong anti-breast cancer activity through the mechanism of apoptosis induction and proliferation inhibition.
8.	The Effect of Modification of Natural Compounds on Anticancer Activity and Their Mechanism of Action	(Amin & Pratama, 2025)	Computational prediction (docking/QSAR), chemical modification synthesis/nanoformulation, validation (in vitro)	Chemical modifications such as functional group substitution and nanoparticle conjugation consistently increase target affinity, improve pharmacokinetic profiles, and enhance mechanisms of action such as caspase activation and decreased VEGF expression.
9.	Molecular docking, ADMET profiling of gallic acid and its derivatives (N-alkyl gallamide) as apoptotic agent of breast cancer MCF-7 Cells	(Arsianti et al., 2022)	Protein-drug interaction analysis, molecular docking (AutoDock), molecular dynamics simulation (YASARA), and ADMET profiles (SwissADME, protox II, pkCSM). Validation was performed through in vitro cytotoxicity assay (MTT method) on MCF-7 cells.	The compounds N-octyl gallamide, N-tert-butyl gallamide, and N-isoamyl gallamide are the best derivatives that interact strongly with the proteins JUN, AKT1, CASP3, and CASP7. All three have been shown to inhibit the growth of MCF-7 breast cancer cells by inducing apoptosis.
10.	Isolation optimization,	(Suthar et al., 2021)	Optimization of the extraction method of	The 3β,22β-diisobutyryloxy derivative (compound 10)

	synthesis, molecular docking and in silico ADMET studies of lantadene a and its derivatives		lantadene A from Lantana camara, synthesis of semi-synthetic derivatives, and molecular docking at the active site of IKK accompanied by in silico ADMET studies.	has the highest affinity for the IKK protein and is predicted to be safe (Ames non-toxic, non-carcinogen) based on the ADMET study.
11.	Marine natural compounds as potential CBP bromodomain inhibitors for treating cancer: an in-silico approach using molecular docking, ADMET, molecular dynamics simulations and MM-PBSA binding free energy calculations	(Ali et al., 2024)	Molecular Docking (PyRx, AutoDock Vina), Molecular Dynamics Simulation (100 ns, GROMACS), ADMET Analysis (SwissADME, ProTox-II), Drug-likeness Test (Lipinski's Rule of Five), In silico	Five marine compounds (stelletin A, ascididemin, neoamphimedine, amphimedine, and deoxytopsentin) have stronger binding affinity than the standard inhibitor 69 A, with ascididemin and stelletin A reaching the highest value of -10.1 kcal/mol. From the results of MD and MM-PBSA simulations, ascididemin was identified as the most potential candidate because it forms the most stable complex, has the lowest binding free energy (-152.656 kJ/mol), and is predicted to be safe and has a high probability as an antineoplastic agent for colorectal and bladder cancer.

Discussion

This study aims to evaluate the role of computational medicinal chemistry approaches, particularly molecular docking, in identifying candidate anticancer compounds from natural products, and to examine the importance of integrating them with ADMET predictions and chemical modification in the compound optimization process. Computational-based approaches are increasingly used in modern drug discovery because they can accelerate the lead compound identification process with better time and cost efficiency than conventional methods (Ferreira et al., 2022).

The results of the literature review show that most of the natural compounds analyzed have potential as anticancer candidates, which is indicated by the low free energy (ΔG) values in the results.*molecular docking*Compounds from the flavonoid, polyphenol, and curcumin derivatives groups have been shown to bind stably to cancer protein targets, such as EGFR and HER2. These interactions generally involve hydrogen bonds, hydrophobic interactions, and van der Waals forces, which contribute to the stability of the ligand-receptor complex (Pinzi & Rastelli, 2022).

However, the results obtained show significant variation in affinity values between studies. This variation is not only caused by differences in the chemical structure of the compounds, but also by differences in the computational approaches used, such as the algorithms used.*docking*, the type of scoring function, and the simulation parameters applied. Furthermore, the choice of target protein

structure and the quality of the crystal structure can also influence docking results. This suggests that molecular docking results are relative and require careful interpretation (Ferreira et al., 2022).

Furthermore, this finding confirms that*molecular docking*has limitations in predicting overall biological activity. Although low ΔG values are often associated with high affinity, this parameter does not always reflect biological effectiveness in complex biological systems. Other factors such as membrane permeability, metabolic stability, and toxicity also play a crucial role in determining the success of a drug candidate (Daina et al., 2022).

In this case, the integration of ADMET predictions becomes crucial. The review results show that most compounds have met several parameters.*drug-likeness*, such as Lipinski's rule, but there are still limitations in pharmacokinetic aspects, such as low oral bioavailability or potential toxicity. This suggests that the drug candidate selection process cannot rely solely on target affinity but must also consider the overall pharmacokinetic profile (Pires et al., 2023).

Furthermore, chemical modification has proven to be an effective strategy for improving the quality of natural product compounds. Several studies have shown that structural derivatization can enhance interactions with protein targets by adding functional groups capable of strengthening hydrogen bonds or increasing lipophilicity. This modification also contributes to improved compound stability and bioavailability, thus increasing their potential for development as drug candidates (Afzal et al., 2022).

However, analysis of the reviewed articles shows that most studies still use a separate approach between*molecular docking*, ADMET prediction, and chemical modification. This lack of integration is one of the obstacles to generating truly optimal compound candidates. However, an integrated approach has been shown to improve predictive accuracy and efficiency in the drug discovery process (Zhang et al., 2023).

In terms of implications, an integrated computational approach holds great potential for supporting the development of natural-based anticancer drugs, particularly in countries with high biodiversity like Indonesia. The use of this method can accelerate the identification of active compounds, reduce the need for expensive experimental testing, andincrease the chances of success at advanced development stages (Atanasov et al., 2022).

However, this study has limitations that need to be considered. First, the data analyzed were derived entirely from literature studies, thus relying heavily on the quality and methodology of previous research. Second, most of the studies reviewed were still in the early stages.*in silico*, so the results do not fully reflect the actual biological conditions. Third, variations in the methods and parameters used in each study can affect the consistency of the results (Newman, 2022).

Based on these limitations, further research is suggested to develop a more comprehensive approach by integrating*molecular docking*, ADMET prediction, and chemical modification within a systematic research framework. Furthermore, experimental validation through in vitro and in vivo testing is essential to ensure the efficacy and safety of compounds. The use of more advanced computational technologies, such as molecular dynamics simulation and artificial intelligence, may also be a promising future research direction in this field (Zhang et al., 2023).

CONCLUSION

Based on the review of 11 selected articles, it can be concluded that computational medicinal chemistry approaches, particularly molecular docking, play a crucial role in the early identification of candidate anticancer compounds from natural products. Most of the studied compounds exhibited good binding affinity to cancer protein targets, as indicated by low free energy (ΔG) values and the formation of stable ligand-receptor interactions.

However, molecular docking results cannot be used as a single indicator for determining potential biological activity, as they are influenced by variations in compound structure, protein targets, and the methods and parameters used. Therefore, integration with ADMET predictions is

crucial for evaluating pharmacokinetic properties and potential toxicity, while chemical modification plays a role in improving the stability, bioavailability, and biological activity of compounds.

Overall, the integrated approach between molecular docking, ADMET prediction, and chemical modification provides a more comprehensive framework in the development of natural product-based anticancer candidates.

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